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# NEUROLOGY

**Cost-effectiveness of preventive treatment of intracranial aneurysms: New data and uncertainties**

Jacoba P. Greving, Gabriël J.E. Rinkel, Erik Buskens and Ale Algra  
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# Cost-effectiveness of preventive treatment of intracranial aneurysms

New data and uncertainties



Jacoba P. Greving, PhD  
Gabriel J.E. Rinkel, MD  
Erik Buskens, MD  
Ale Algra, MD

Address correspondence and reprint requests to Dr. Jacoba P. Greving, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands  
J.P.Greving@umcutrecht.nl

## ABSTRACT

**Background:** Previous modeling studies on treatment of unruptured intracranial aneurysms largely disregarded detailed data on treatment risks and omitted several factors that could influence cost-effectiveness. We performed a cost-effectiveness analysis of surgical and endovascular treatment of unruptured aneurysms for different rupture rates and life expectancies, and assessed the influence of excess mortality risks in these persons, de novo development of aneurysms, and utility of awareness of having an untreated aneurysm, and also identified important factors for which data are lacking.

**Methods:** We used a Markov model to compare surgical, endovascular, and no treatment of unruptured intracranial aneurysms. Inputs for the model were taken mainly from meta-analyses. Direct medical costs were derived from Dutch cost studies and expressed in 2005 Euros. We performed sensitivity analyses to evaluate model robustness.

**Results:** For 50-year-old patients, treatment of unruptured aneurysms is cost-effective for all rupture rate scenarios between 0.3% and 3.5%/year. In 70-year-old patients, treatment is not cost-effective in men with rupture rates  $\leq 1\%$ /year and women with rupture rates  $\leq 0.5\%$ /year. With lower utility of awareness of an untreated aneurysm, the cost-effectiveness of treatment strongly increased. The effect of excess mortality risks on the incremental cost-effectiveness ratios was modest. The risk of formation of new aneurysms had no relevant impact.

**Conclusions:** Patients' life expectancy, risk of rupture, and utility of awareness of an untreated aneurysm mainly define cost-effectiveness. However, important uncertainties remain on the rupture risk according to size and location of the aneurysm and on the utility of awareness of untreated aneurysm. More data on these factors are needed to define and individualize cost-effectiveness analyses. *Neurology*® 2009;73:258-265

## GLOSSARY

**ICER** = incremental cost-effectiveness ratios; **ISUIA** = International Study of Unruptured Intracranial Aneurysms; **QALY** = quality-adjusted life-year; **SAH** = subarachnoid hemorrhage.

Despite modern microsurgical techniques and rapidly developing endovascular treatment options, nearly half of the patients with a subarachnoid hemorrhage (SAH) from a ruptured aneurysm die within the first weeks after the hemorrhage. Over 10% of all patients with SAH die before reaching the hospital and cannot be salvaged.<sup>1</sup> Patients who reach the hospital alive may already be in a poor clinical condition from the initial bleeding and are at risk of complications such as rebleeding, secondary ischemia, and systemic complications.<sup>2,3</sup> Prevention of aneurysmal rupture therefore seems an attractive option, but surgical or endovascular occlusion of intracranial aneurysms themselves carry a risk of serious complications.

In 2003, the International Study of Unruptured Intracranial Aneurysms (ISUIA) investigators reported prospective data on the management of unruptured intracranial aneurysms.<sup>4</sup> However, there remains controversy about whether unruptured intracranial aneurysms should be treated, and

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From the Julius Center for Health Sciences and Primary Care (J.P.G., A.A.) and Department of Neurology and Neurosurgery, Rudolf Magnus Institute of Neuroscience (G.J.E.R., A.A.), University Medical Center Utrecht; and Department of Epidemiology (E.B.), University Medical Center Groningen, University of Groningen, The Netherlands.

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if so which method of aneurysm occlusion (surgical clipping or endovascular coiling) should be offered.<sup>5,6</sup> There are no data from randomized clinical trials yet. One trial (TEAM) has started recently, but even if such a trial will provide an answer eventually, for the next decade we have to rely on other sources on which to base our decisions. Because treatment choice requires a comparison of acute treatment-related risks and future rupture risk, decision analysis may be an appropriate way to gain the best possible insight into the balance of risks and benefits. Several such decision and cost-effectiveness analyses have been performed.<sup>7-11</sup> However, in these analyses, comparisons among surgical clipping, endovascular coiling, and no treatment were based on earlier estimates of complications risks or data derived from the ISUIA only.<sup>4</sup> Furthermore, the risk of formation and rupture of recurrent and de novo aneurysms were not included in these models.

The objective of this study was to evaluate and update estimates of cost-effectiveness of surgical and endovascular treatment of unruptured aneurysms for different rupture rates and different life expectancies. Moreover, we assessed the influence of excess mortality risks in these persons, de novo aneurysm formation and utility of awareness of having an untreated aneurysm, and also identified factors that are pivotal in the analyses for which data are lacking.

**METHODS Model structure.** We developed a Markov model to estimate the expected lifetime costs and quality-adjusted life-years (QALYs) after surgical clipping, endovascular coiling, and no treatment of unruptured intracranial aneurysms. The model was designed to simulate cohorts of patients with unruptured aneurysms with various levels of rupture risk. The model comprises eight health states: well with a treated or untreated aneurysm, well with a recurrent or de novo aneurysm, well treated after SAH, disabled (after SAH or after treatment), and dead (figure e-1 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)). There are unique costs and quality of life values (utilities) associated with each health state. Analyses were continued until all individuals in the hypothetical cohorts had died from their aneurysm or other causes.

**Preventive treatment option.** Patients who underwent preventive occlusion may have died during or immediately after the intervention, survived with a mild or moderate to severe disability, or survived with normal neurologic function. Surgical clipping was assumed to eliminate the risk of SAH at least in the first year. However, a small possibility of regrowth and rupture of the clipped aneurysm remained in subsequent years. Endovascular coiling was assumed to provide partial protection against aneurysm rupture, since incomplete occlusion was obtained in a substantial proportion

of aneurysms. Also, reopening of the aneurysm has been shown to occur over time. All persons with a treated aneurysm, either by clipping or coiling, still carried a risk of SAH because of formation of de novo aneurysms over time.

**No preventive treatment option.** The no-treatment option did not involve the initial procedure-related risk, but obviously there was a persistent risk of aneurysm rupture. All patients in whom an SAH developed were supposed to undergo optimal treatment. Patients with SAH may die before hospitalization or during or immediately after treatment for SAH, may survive with a mild or moderate to severe disability, or may completely recover after SAH. All surviving patients still carried a risk of SAH because of formation of de novo aneurysms over time.

**Model estimates: Clinical assumptions.** We retrieved the transition probabilities for our model from the literature (table 1).

**Risk of rupture in untreated aneurysms.** The reported rupture risks of an unruptured intracranial aneurysm vary from nil to 2.3% per year.<sup>4,12-17</sup> A recent meta-analysis reported an overall rupture risk of 0.9% per year.<sup>17</sup> Aneurysm rupture risks vary depending on patient characteristics (age, gender) and aneurysm characteristics (size, location) and whether there is a history of SAH from a different aneurysm.<sup>17</sup> To account for variable aneurysm characteristics, we modeled eight different rupture risk scenarios (range, 0.3–3.5% per year).

**Risks of complications from preventive treatment.** We used both ISUIA data and results from reviews on mortality and morbidity rates of preventive treatment in general.<sup>4,18,19</sup> We used a treatment-related mortality rate of clipping of 1.8% and a morbidity rate of 5.6%.<sup>4,18</sup> For coiling, we used a treatment-related mortality rate of 0.6% and a morbidity rate of 7%.<sup>19</sup> We assumed that half of the patients with surgical morbidity and one-third of patients with endovascular morbidity became moderately to severely disabled.<sup>4,18,19</sup>

**Risk of development of a regrowth, reopening, or de novo aneurysm.** After clipping, a regrowth rate of 0.3 to 0.5% per year has been reported.<sup>20-23</sup> We used a regrowth rate of 0.4% per year in the first 10 years after clipping. The main concerns with endovascular treatment are the substantial proportion of aneurysms that are incompletely occluded initially and the possibility of reopening of the aneurysm over time. Reported aneurysmal recurrence rates were 14% in the first 12 months, 5% in the second year, and 2% in the third year after initial coiling treatment.<sup>24,25</sup> Half of the patients with a recurrence were assumed to receive additional treatment.<sup>24,25</sup> We assumed that additional treatment eliminated the risk of subsequent SAH. The risk of rupture for aneurysms that did not undergo re-treatment was assumed to be equal to the risk of the initially coiled aneurysm. The development of de novo aneurysms varied between 0.5 and 0.9% per year in low-risk populations.<sup>21,22,26</sup> We used a de novo formation rate of 0.5% per year.

**Risk of rupture of regrowth, reopening, or de novo aneurysms.** The reported rupture risks for additional aneurysms do not differ from rupture rates of incidentally found unruptured aneurysms.<sup>17,27</sup> Therefore, we used similar rupture rates for incidental and recurrent aneurysms. Since we did not take into account nor were interested in the possible effects of repeated diagnostic follow-up, we used a constant average rupture risk (i.e., 0.9%/year) for de novo aneurysms.<sup>17</sup> We assumed that a regrowth or de novo aneurysm could not rupture until 5 years after development.<sup>22</sup>

**Risk of death and disability.** Age- and sex-specific annual mortality rates were taken from national life tables.<sup>28</sup> The reported case fatality rates after SAH vary from 21% to 44%.<sup>23</sup> We assumed a case fatality rate of 35%, that 9% who survived their bleed became permanently severely disabled, and that 15% became mildly dis-

**Table 1** Transition probabilities, utilities, and costs used in the Markov model

| Variables                               | Estimate                          | Range     | Distribution | Data source*       | Reference  |
|-----------------------------------------|-----------------------------------|-----------|--------------|--------------------|------------|
| <b>Surgical clipping</b>                |                                   |           |              |                    |            |
| Procedure-related death                 | 1.8%                              | 1.2–2.5%  | Beta         | Meta-analysis      | 4, 18      |
| Permanent moderate to severe disability | 2.8%                              | 2.2–3.5%  | Beta         | Meta-analysis      | 4, 18      |
| Permanent mild disability               | 2.8%                              | 2.2–3.5%  | Beta         | Meta-analysis      | 4, 18      |
| Regrowth rate after clipping/year       | 0.4%                              | 0.3–0.5%  | Uniform      | Cohort study       | 20, 21, 23 |
| <b>Endovascular coiling</b>             |                                   |           |              |                    |            |
| Procedure-related death                 | 0.6%                              | 0.2–1.0%  | Beta         | Meta-analysis      | 4, 19      |
| Permanent moderate to severe disability | 2.2%                              | 1.3–3.4%  | Beta         | Meta-analysis      | 4, 19      |
| Permanent mild disability               | 4.8%                              | 3.4–6.5%  | Beta         | Meta-analysis      | 4, 19      |
| <b>Reopening</b>                        |                                   |           |              |                    |            |
| First year after coiling                | 14%                               | 11–17%    | Uniform      | Cohort study       | 24, 25     |
| Second year after coiling               | 5%                                | 3–7%      | Uniform      | Cohort study       | 24, 25     |
| Third year after coiling                | 2%                                | 1–3%      | Uniform      | Cohort study       | 24, 25     |
| <b>De novo aneurysms</b>                |                                   |           |              |                    |            |
| De novo aneurysm formation/year         | 0.5%                              | 0.3–0.8%  | Beta         | Cohort study       | 21, 22, 26 |
| Risk of rupture de novo/year            | 0.9%                              | 0.7–1.0%  | Beta         | Meta-analysis      | 17         |
| <b>SAH</b>                              |                                   |           |              |                    |            |
| Death before reaching the hospital      | 12%                               | 11–14%    | Beta         | Meta-analysis      | 1          |
| Case fatality (at 1 yr)                 | 35%                               | 25–45%    | Beta         | Meta-analysis      | 2, 3       |
| Moderate to severe disability           | 9%                                | 7–11%     | Beta         | Meta-analysis      | 2, 3       |
| Mild disability                         | 15%                               | 13–17%    | Beta         | Meta-analysis      | 2, 3       |
| Mortality                               | Age-/sex-specific mortality rates |           |              |                    |            |
| All-cause mortality                     |                                   |           |              |                    | 28         |
| SMR moderate to severe disability       | 2.0                               | 1.0–3.0   | Triangular   | Cohort study       | 29         |
| <b>Utilities</b>                        |                                   |           |              |                    |            |
| Permanent moderate to severe disability | 0.41                              | 0.25–0.65 | Triangular   | Review             | 30         |
| Permanent mild disability               | 0.72                              | 0.65–0.80 | Triangular   | Review             | 30         |
| Awareness of an untreated aneurysm      | 0.92                              | 0.87–1.0  | Triangular   | Case-control study | 31         |
| <b>Costs (in 2005 Euros)</b>            |                                   |           |              |                    |            |
| Preventive clipping                     | 8,672                             | —         | —            | Cohort study       | 32         |
| Preventive coiling                      | 10,440                            | —         | —            | Cohort study       | 32         |
| Treatment after SAH                     | 26,561                            | —         | —            | Cohort study       | 33         |
| Death                                   | 2,579                             | —         | —            | Expert opinion     | 34         |
| Moderate to severe disability           | 20,194                            | —         | —            | Cost study         | 34         |
| Mild disability                         | 1,038                             | —         | —            | Cost study         | 34         |

\*When multiple publications were used, the study type with the strongest study design was mentioned.  
SMR = standardized mortality rate; SAH = subarachnoid hemorrhage.

abled.<sup>23</sup> The proportion of patients with SAH who died before receiving medical attention was assumed to be 12%.<sup>1</sup> Patients who survived their bleed and were left disabled experience excess mortality compared with the general population.<sup>29</sup> We therefore assumed a twofold increased risk of dying in moderately to severely disabled patients. Patients with an unruptured aneurysm may also have a reduced life expectancy due to the presence of vascular disease. We accounted for this in the sensitivity analysis.

**Utilities.** Benefits were measured in QALYs. Utility weights for the health states minor disability (0.72) and moderate to severe

disability (0.41) were derived from data published in the literature.<sup>30</sup> Awareness of having an untreated aneurysm that may at any time rupture with inherent catastrophic effects may negatively influence quality of life. For this impact of the awareness of having an untreated aneurysm, we estimated a utility of 0.92.<sup>31</sup>

**Costs.** We conducted our economic analysis from the health-care payer perspective. A recent Dutch study details the direct costs associated with preventive aneurysm occlusion.<sup>32</sup> From these data, we estimated that the costs of these treatments and the control visits and examinations were €8,672 for clipping and



**Table 2** Simulated lifetime effects (mean of 2,000 iterations in cohorts of 50,000 patients) in each treatment strategy for formation and rupture of aneurysms with a rupture rate of 1%/year

| Age, y                        | Men  |      | Women |      |
|-------------------------------|------|------|-------|------|
|                               | 50   | 70   | 50    | 70   |
| <b>Formation of aneurysms</b> |      |      |       |      |
| <b>De novo aneurysm</b>       |      |      |       |      |
| No treatment                  | 11.4 | 5.1  | 13.1  | 6.6  |
| Surgical treatment            | 11.2 | 4.8  | 12.9  | 6.4  |
| Endovascular treatment        | 11.4 | 4.9  | 13.2  | 6.5  |
| <b>Aneurysm regrowth</b>      |      |      |       |      |
| Surgical treatment            | 3.4  | 2.8  | 3.5   | 3.1  |
| <b>Aneurysm reopening</b>     |      |      |       |      |
| Endovascular treatment        | 19.8 | 19.4 | 19.8  | 19.6 |
| <b>Future SAH risk</b>        |      |      |       |      |
| No treatment                  | 22.8 | 10.2 | 26.3  | 13.3 |
| Surgical treatment            | 1.6  | 0.3  | 2.1   | 0.5  |
| Endovascular treatment        | 3.4  | 1.3  | 4.1   | 1.7  |

Values are percentages.  
SAH = subarachnoid hemorrhage.

€10,440 for coiling. Costs of SAH in the first year after diagnosis were derived from a multicenter study in The Netherlands and were estimated at €26,561.<sup>33</sup> The annual costs of care for disabled patients after preventive treatment or SAH were taken from data on long-term care in stroke patients.<sup>34</sup> The model does not account for any costs of diagnostic follow-up in the no-treatment arm. All cost estimates were updated to 2005 Euros based on Dutch inflation indices (<http://statline.cbs.nl>).

**Cost-effectiveness and sensitivity analysis.** We modeled eight different rupture risk scenarios (ranging from 0.3 to 3.5%) for 50-year-old and 70-year-old men and women separately. Although standard practice in cost-effectiveness analysis is to compare each treatment with the next best option, we chose to compare both preventive treatments with no treatment, as our aim in this study was to decide which unruptured intracranial aneurysms should be treated. Incremental cost-effectiveness ratios (ICER) were defined as the difference in costs divided by the difference in QALYs. Treatment was considered cost-effective at an ICER of €20,000 per QALY gained. Both costs and effects were discounted at 4%.

Extensive sensitivity analyses were performed by altering the input values for individual variables, with plausible ranges of values as given in table 1. To assess the combined uncertainty embedded in all input variables simultaneously, we performed probabilistic sensitivity analyses with Monte Carlo simulation. For each simulation of the model, a value of each input variable was selected randomly from its distribution.<sup>35</sup> Additionally, we conducted scenario analyses on 1) increase in surgical risk of death or severe disability for 70-year-old patients, 2) excess mortality for patients with unruptured aneurysms, and 3) the impact of indirect costs according to the friction cost method.<sup>4,29,36</sup> Patients were assumed to be absent from work for 4 weeks after clipping and 1.5 weeks after coiling. Dutch workforce participation rates were obtained from Dutch Bureau of Statistics data (<http://statline.cbs.nl>). All analyses were conducted in TreeAge (TreeAge Pro Suite 2008, Williamstown, VA).

**RESULTS** Treatment of intracranial unruptured aneurysms reduced the risk of future SAH. For aneurysms with a rupture risk of 1%/year in 50-year-old men, the predicted probability of SAH during the remaining lifetime was 22.8% without preventive treatment. This risk was only 1.6% after clipping and 3.4% after coiling (table 2). For 70-year-old men, the lifetime risk of SAH decreased from 10.2% in case no treatment would be offered to 0.3% after clipping and 1.3% after coiling. The predicted probability of de novo aneurysm formation decreased with age from 11% to 5% in men initially aged 50 vs 70 years. A regrowth was predicted to occur in 3% of all clipped patients and a reopening occurred in approximately 20% of all coiled patients. The predicted lifetime risks of SAH and de novo aneurysm formation were slightly higher in women, since women have higher life expectancies than men.

**Cost-effectiveness analyses.** For 50-year-old men, both preventive treatments resulted in a net QALY gain ranging from 0.9 to 2.3 QALY for rupture rates between 0.3% and 3.5%/year (table 3). The magnitude of benefit of treatment decreased with age, but was still present for patients aged 70 years (net benefit ranging from 0.4 to 0.9 QALY). In general, the benefit of treatment was somewhat greater in women: net benefit ranged from 1.0 to 2.7 QALY in 50-year-old women and ranged from 0.6 to 1.2 QALY in 70-year-old women (table e-1). Both treatments were cost-effective for all rupture rate scenarios between 0.3% and 3.5% per year in 50-year-old men and women (table 3 and table e-1). For rupture rates of 0.3%/year in 50-year-old men, ICERs were €19,818/QALY for clipping and €18,588/QALY for coiling. For higher rupture rates of 3.5%/year, the ICERs decreased considerably to €940/QALY for clipping and €2,194/QALY for coiling. For 70-year-old men with a rupture rate up to 1%/year, no treatment appeared the preferred option. Either treatment would become cost-effective with rupture rates surpassing 1%/year for men and 0.5%/year for women.

**Sensitivity analyses.** These results were sensitive to 1) the utility of awareness of an untreated aneurysm and 2) the treatment-related moderate to severe disability. With increasing disutility, the cost-effectiveness of treatment substantially improved (figure). Increasing the surgical risk of death or moderate to severe disability for 70-year-old patients resulted in considerably higher ICERs (for example, at a twofold higher risk of poor surgical outcome, the ICER increased from €15,491/QALY to approximately €66,000/QALY in 70-year-old men with a rupture rate of 1.5%/year), making clipping cost-ineffective

**Table 3** Simulated lifetime effects, costs, and cost-effectiveness (mean of 2,000 iterations in cohorts of 50,000 patients) of surgical clipping and endovascular coiling compared with no treatment for 50-year-old and 70-year-old men with an unruptured intracranial aneurysm

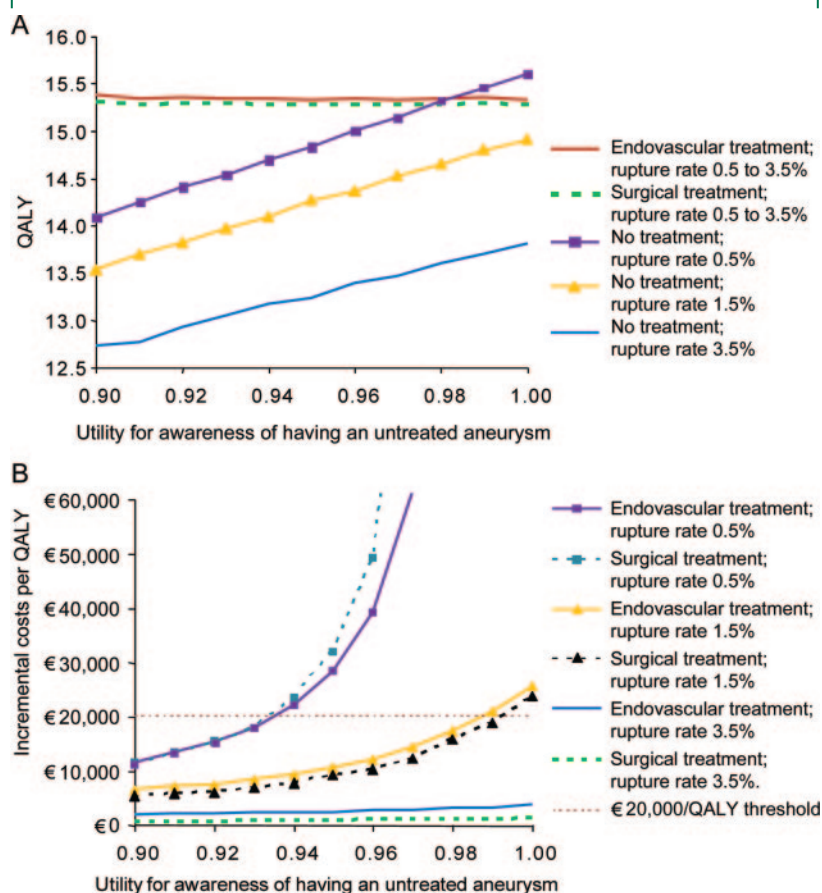
| Age and rupture risk, %/y | Future SAH risk, % |          |         | QALY, y          |                  |                  | Costs, €               |                        |                        | Incremental costs per QALY*, €/QALY |                         |  |
|---------------------------|--------------------|----------|---------|------------------|------------------|------------------|------------------------|------------------------|------------------------|-------------------------------------|-------------------------|--|
|                           | No treatment       | Clipping | Coiling | No treatment     | Clipping         | Coiling          | No treatment           | Clipping               | Coiling                | Clipping vs no treatment            | Coiling vs no treatment |  |
| <b>50 years</b>           |                    |          |         |                  |                  |                  |                        |                        |                        |                                     |                         |  |
| 0.3                       | 8.3                | 1.2      | 1.8     | 14.5 (14.5-14.6) | 15.3 (15.1-15.5) | 15.4 (15.2-15.6) | 2,825 (2,590-3,090)    | 18,164 (16,208-20,478) | 19,804 (17,095-23,454) | 19,818 (15,121-27,520)              | 18,588 (13,776-27,134)  |  |
| 0.5                       | 12.7               | 1.3      | 2.3     | 14.4 (14.3-14.5) | 15.3 (15.1-15.4) | 15.4 (15.2-15.6) | 3,904 (3,565-4,300)    | 18,176 (16,168-20,370) | 19,939 (17,253-23,406) | 15,886 (12,194-21,827)              | 15,673 (11,460-22,681)  |  |
| 1.0                       | 22.8               | 1.6      | 3.4     | 14.1 (13.9-14.3) | 15.3 (15.1-15.4) | 15.4 (15.2-15.5) | 6,435 (5,797-7,168)    | 18,247 (16,238-20,492) | 20,214 (17,625-23,723) | 9,964 (7,478-13,473)                | 10,777 (7,864-15,411)   |  |
| 1.5                       | 31.5               | 1.8      | 4.3     | 13.8 (13.6-14.1) | 15.3 (15.1-15.4) | 15.3 (15.2-15.5) | 8,761 (7,882-9,913)    | 18,281 (16,331-20,587) | 20,479 (17,663-24,146) | 6,515 (4,573-9,068)                 | 7,708 (5,275-11,506)    |  |
| 2.0                       | 39.1               | 2.1      | 5.2     | 13.6 (13.3-13.9) | 15.3 (15.1-15.4) | 15.3 (15.1-15.5) | 10,854 (9,778-12,156)  | 18,305 (16,358-20,706) | 20,661 (17,910-24,183) | 4,373 (2,894-6,401)                 | 5,648 (3,744-8,612)     |  |
| 2.5                       | 45.7               | 2.2      | 5.9     | 13.3 (12.9-13.7) | 15.3 (15.1-15.4) | 15.3 (15.1-15.4) | 12,780 (11,416-14,309) | 18,327 (16,330-20,663) | 20,893 (18,180-24,363) | 2,876 (1,644-4,517)                 | 4,196 (2,426-6,728)     |  |
| 3.0                       | 51.5               | 2.4      | 6.6     | 13.1 (12.7-13.5) | 15.3 (15.1-15.4) | 15.2 (15.0-15.4) | 14,549 (13,040-16,312) | 18,417 (16,429-20,778) | 21,121 (18,299-24,522) | 1,809 (678-3,299)                   | 3,107 (1,596-5,342)     |  |
| 3.5                       | 56.5               | 2.6      | 7.2     | 12.9 (12.4-13.4) | 15.3 (15.1-15.4) | 15.2 (15.0-15.4) | 16,228 (14,460-18,183) | 18,419 (16,516-20,719) | 21,249 (18,476-24,751) | 940 (-119-2,251)                    | 2,194 (727-4,187)       |  |
| <b>70 years</b>           |                    |          |         |                  |                  |                  |                        |                        |                        |                                     |                         |  |
| 0.3                       | 3.3                | 0.2      | 0.5     | 8.0 (8.0-8.1)    | 8.4 (8.3-8.5)    | 8.5 (8.4-8.6)    | 2,440 (2,361-2,548)    | 14,287 (13,232-15,671) | 16,592 (15,280-18,365) | 32,317 (25,101-45,237)              | 31,457 (23,955-44,221)  |  |
| 0.5                       | 5.4                | 0.2      | 0.7     | 8.0 (7.9-8.0)    | 8.4 (8.3-8.5)    | 8.5 (8.4-8.6)    | 2,891 (2,770-3,051)    | 14,275 (13,208-15,671) | 16,617 (15,246-18,476) | 27,996 (21,829-38,165)              | 28,239 (21,902-39,068)  |  |
| 1.0                       | 10.2               | 0.3      | 1.3     | 7.9 (7.8-7.9)    | 8.4 (8.3-8.5)    | 8.5 (8.3-8.5)    | 3,967 (3,744-4,261)    | 14,299 (13,211-15,672) | 16,744 (15,415-18,522) | 20,459 (16,067-27,048)              | 22,328 (17,437-30,219)  |  |
| 1.5                       | 14.7               | 0.4      | 1.8     | 7.8 (7.7-7.9)    | 8.4 (8.3-8.5)    | 8.4 (8.3-8.5)    | 4,998 (4,690-5,396)    | 14,294 (13,220-15,633) | 16,839 (15,465-18,644) | 15,491 (12,268-20,146)              | 18,076 (14,148-24,581)  |  |
| 2.0                       | 19.0               | 0.4      | 2.2     | 7.7 (7.6-7.8)    | 8.4 (8.3-8.5)    | 8.4 (8.3-8.5)    | 5,965 (5,584-6,450)    | 14,302 (13,226-15,682) | 16,945 (15,607-18,778) | 12,086 (9,488-16,079)               | 14,981 (11,625-20,304)  |  |
| 2.5                       | 22.9               | 0.5      | 2.7     | 7.6 (7.5-7.7)    | 8.4 (8.3-8.5)    | 8.4 (8.3-8.5)    | 6,890 (6,428-7,561)    | 14,329 (13,246-15,828) | 17,071 (15,693-18,922) | 9,636 (7,421-12,723)                | 12,660 (9,696-17,141)   |  |
| 3.0                       | 26.6               | 0.5      | 3.1     | 7.5 (7.4-7.7)    | 8.4 (8.3-8.5)    | 8.4 (8.3-8.5)    | 7,771 (7,223-8,476)    | 14,322 (13,290-15,677) | 17,113 (15,792-19,033) | 7,648 (5,787-10,294)                | 10,618 (8,077-14,360)   |  |
| 3.5                       | 30.1               | 0.6      | 3.5     | 7.5 (7.3-7.6)    | 8.4 (8.3-8.5)    | 8.4 (8.3-8.5)    | 8,613 (7,960-9,496)    | 14,352 (13,289-15,759) | 17,247 (15,863-19,159) | 6,164 (4,630-8,493)                 | 9,156 (6,855-12,734)    |  |

Confidence intervals were derived from the Monte Carlo simulation.

\*Both treatments were compared with no treatment.

SAH = subarachnoid hemorrhage; QALY = quality-adjusted life-year.

**Figure** Sensitivity analyses on the effect of decreasing utility for awareness of having an untreated aneurysm (horizontal axis) and annual rupture rate on quality-adjusted life-year (QALY) and incremental costs per QALY



For a 50-year-old man, aneurysm treatment was more effective than no treatment unless the rupture rate was 0.5%/year and the utility for being aware of an untreated aneurysm was greater than 0.98. The incremental cost-effectiveness ratios for both treatments were below the €20,000 per QALY threshold for rupture rates of 0.5%/year and utilities lower than 0.94 for awareness of having an untreated aneurysm.

for older patients. Assuming that patients with an unruptured aneurysm have a twofold increased risk of dying compared with the general population due to the presence of vascular disease reduced the cost-effectiveness of treatment slightly (for example, the ICER for clipping increased from €19,818 to €22,298 in 50-year-old men with a rupture rate of 0.3%/year). Taking indirect costs into consideration, the ICERs increased somewhat (€24,629/QALY for clipping and €20,170/QALY for coiling in 50-year-old men with a rupture rate of 0.3%/year). The remaining probability estimates, including development of de novo and recurrent aneurysms, had no relevant impact on the incremental cost-effectiveness ratios when varied over a wide range.

**DISCUSSION** This cost-effectiveness analysis showed that preventive treatment of intracranial aneurysms is cost-effective in middle-aged patients for all rupture rate scenarios between 0.3% and 3.5%

**Table 4** What is new in this cost-effectiveness analysis and remaining areas of uncertainty

**What is new?**

- Use of complications and risks of clipping and coiling not only based on ISUIA data
- Risk formation and rupture of recurrent and de novo aneurysms taken into account
- Use of a utility for awareness of an untreated aneurysm based on a study that assessed the perceived burden of finding small aneurysms that are left untreated
- Costs of repeated endovascular treatments taken into account
- Use of recent, accurate cost estimates of preventive clipping and coiling
- Identification of areas of uncertainty

**Remaining areas of uncertainty**

- Reliable estimation of utility of awareness of untreated aneurysm for presenting person
- Risk of aneurysm rupture according to size and location: multivariable estimates needed
- Treatment-related complication risks according to age and aneurysm size and location
- Natural excess mortality in persons with unruptured aneurysms
- Rebleeding risk after incomplete endovascular treatment

ISUIA = International Study of Unruptured Intracranial Aneurysms.

per year. Surgical and endovascular treatments have both a substantial treatment benefit and are generally equally cost-effective. For 70-year-old patients, treatment of unruptured aneurysms is no longer cost-effective in men with rupture rates  $\leq 1\%$ /year and women with rupture rates  $\leq 0.5\%$ /year. Overall, the analysis implies that patients' life expectancy, risk of rupture, and utility of awareness of an untreated aneurysm mainly define when treatment becomes cost-effective. The effect of excess mortality risks, if present in these persons at all, on the incremental cost-effectiveness ratios was small. The risk of formation of recurrent and de novo aneurysms had no relevant impact on the cost-effectiveness ratios.

In the current cost-effectiveness analysis, several new aspects were introduced to overcome a number of potential limitations in existing studies (table 4, top). Previous cost-effectiveness analyses have demonstrated that treatment of unruptured aneurysm in 50-year-old patients becomes cost-effective when the rupture rate is about 1%/year.<sup>7,8</sup> Another study reported that treatment was cost-effective for aneurysms that are  $\geq 13$  mm located in the anterior circulation and 7- to 12-mm aneurysms located in the posterior location, i.e., aneurysms with a yearly rupture rate above 3%.<sup>11</sup> However, those findings were based on earlier estimates of complications, risks, or results of the prospective ISUIA data only.<sup>4</sup>



Despite the merits of being the largest prospective study on risk of rupture of unruptured intracranial aneurysms, the ISUIA study has several important weaknesses and therefore should be interpreted with caution.<sup>5,6</sup> Furthermore, in previous cost-effectiveness analyses of unruptured aneurysm treatment, there was a tendency for endovascular treatment to be more cost-effective than surgical treatment.<sup>9,11</sup> However, these studies did not consider the costs of additional treatments and therefore underestimated the costs of endovascular treatment. In addition, more accurate cost estimates for surgical and endovascular treatments (in particular the higher costs of coils) have become available.<sup>32</sup> Furthermore, the risk of formation and rupture of recurrent and de novo aneurysms were not included in these models.

Our study has certain limitations. Since it is unclear how incomplete endovascular occlusion affects rupture risk, we assumed a rupture risk for an incompletely occluded aneurysm or reopened aneurysm that was equal to rupture risk of the initially coiled aneurysm. Health benefits of endovascular treatment may, therefore, have been underestimated. Second, we assumed that all unruptured intracranial aneurysms had the same treatment-related morbidity and mortality rates, while the ISUIA reported that treatment outcomes varied depending on aneurysm size and location.<sup>4</sup> Furthermore, surgical outcomes seem to be dependent on patient age.<sup>4</sup> Notably, as the risk of surgery increases with age, the preferable method for treatment of unruptured aneurysms for older patients would be endovascular treatment. However, this also depends on the experience and results of treating clinics. Third, we assumed that preventive treatment costs were constant across different rupture rate scenarios (i.e., for smaller vs larger aneurysms), because size-specific data for treatment costs were lacking. Therefore, costs and cost-effectiveness ratios may in fact be somewhat higher for treatment of larger aneurysms, but somewhat lower for smaller aneurysms. Fourth, health care costs in the United States and other countries may be different from Dutch cost estimates. A global increase in costs, e.g., in accordance with differences between US and Dutch cost estimates, would result in higher cost-effectiveness ratios, which would reduce the yield for preventive treatment in small aneurysms. Finally, we conducted our economic analysis from the healthcare payer perspective (including only direct medical costs). With a societal perspective (additionally including indirect costs), the incremental cost-effectiveness estimates changed marginally.

We identified several remaining areas of uncertainty (table 4, bottom). Our results were highly sensitive to the utility of awareness of an untreated

aneurysm. Only a slight decrease in quality of life from the awareness of an untreated aneurysm led to a substantial increase in the incremental cost-effectiveness ratio of treatment. Regrettably, little is known about the utility in patients who are aware of an increased health risk, but refrained from treatment, and about modifying factors. Aneurysm rupture risks are known to increase with larger size, posterior circulation aneurysms, older age, and female gender.<sup>17</sup> Also, it is likely that some of these characteristics are not independent. However, since data currently available in the literature did not allow performing multivariable analysis, uncertainty in the estimation of individual aneurysmal rupture risk will remain. Questions about excess mortality in persons with unruptured aneurysms and rupture risk after incomplete coiling remain unanswered, but their influence on cost-effectiveness will be limited.

Our results may help physicians and patients in deciding whether preventive aneurysm occlusion would be justified based on the estimated rupture risk and perceived burden of an untreated aneurysm. For more refined cost-effectiveness analyses and individualized risk estimates, more data on risk of rupture according to size and location of aneurysms and on the utility of the awareness of an untreated aneurysm are needed.

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**Cost-effectiveness of preventive treatment of intracranial aneurysms: New data and uncertainties**

Jacoba P. Greving, Gabriël J.E. Rinkel, Erik Buskens and Ale Algra  
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